



Serum adiponectin and insulin sensitivity affect by aerobic exercise program in patients with type 2 diabetes mellitus

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Received: 22 August 2012

Revised: 06 September 2012

Accepted: 07 September 2012

Key words: Diabetes, exercise training, weight reduction, adiponectin.

Abstract

Obesity and type 2 diabetic are strongly related to cardiovascular disease. The objective of this study was to investigation whether a long time aerobic training program affects adiponectin and insulin sensitivity in patients with type 2 diabetic. A total of 30 obese males with type 2 diabetic were randomly assigned to either a 3-month aerobic exercise training program (3 sessions/wk) designated as experimental group, or to the control group. Also, 15 non-obese adult male participated as healthy group in the study to compare the baseline levels of biochemical indexes with that of diabetic patients. Fasting adiponectin, glucose, insulin sensitivity (HOMA-IS) were measured at baseline and at the end of the study in all diabetic patients. Statistical analyses was performed with the SPSS software using a T- test method to comparing of baseline between diabetic and healthy subjects, and determine the effect aerobic exercise on all variables in experimental group of diabetic. At baseline, serum adiponectin and insulin sensitivity in diabetic patients was significantly lower and fasting glucose was significantly higher than healthy subjects ($P < 0.05$). Serum adiponectin and insulin sensitivity following aerobic exercise significantly increased in the experimental group ($P < 0.05$). In addition, exercise training reduced fasting glucose, body weight, body fat percentage and body mass index in this group ($P < 0.05$). All variables remained without change in control group ($p > 0.05$). Our study shows that aerobic exercise-induced weight loss increases adiponectin as anti-diabetic cytokine and improves insulin action in patients with type 2 diabeti.

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Introduction

Cardiovascular diseases represent the most important mortality factors in current worldwide (Ford *et al.*, 2003). Lipid disorders, in metabolic syndrome and diabetes are precipitating factors of heart disease. Inflammation caused by pre-inflammatory cytokines is among the main factors of metabolic syndrome and type 2 diabetes (Ford *et al.*, 2003). Recently, the role of hormones secreted from adipose tissue as regulators of skeletal muscle metabolism and the development of insulin resistance and ultimately type 2-diabetes have been a focus for many researchers today. Adiponectin is an anti-inflammatory cytokine with 30 kDa molecular weight that is secreted mainly by adipose tissue (Bruun *et al.*, 2003) and unlike other adipokines, its concentration is reduced in obesity. Adiponectin is at present identified as one of the most important adipocytokines to understand better the relationship between obesity and such metabolic diseases as type 2 diabetes (Ahima, 2006; Pischon *et al.*, 2006). Research studies have revealed that this peptide hormone has anti-diabetic (Lara-Castro *et al.*, 2006), anti-inflammatory and anti-atherogenic properties (Ajuwon *et al.*, 2005). The findings of epidemiological studies have shown that plasma adiponectin in patients with cardiovascular diseases (Ouchi *et al.*, 2003), the obese and type 2 diabetics (Ahima, 2006) is reduced. Adiponectin concentration has a negative correlation with insulin resistance and blood glucose concentrations (Pischon *et al.*, 2006).

There are also conflicting findings on the characteristics of adiponectin and its relationship with other metabolic and hormonal factors. In a recent study, no correlation between baseline levels of adiponectin and visceral fat tissue, and other factors was observed in obese women (Ibáñez *et al.*, 2010). Increased adiponectin levels and insulin sensitivity is usually observed after decrease of body fat levels through proper diet (Ibáñez *et al.*, 2010). Interferences of reduced inflammation associated with obesity, increase systemic adiponectin levels (Puglisi *et al.*, 2008). Adiponectin increases in

response to diet-induced weight loss, of course some researches demonstrated that proper weight loss for change in adiponectin levels should be more than 10 percent of the initial weight (Madsen *et al.*, 2008; Ng *et al.*, 2007).

Exercise effect on adiponectin levels is not yet fully clear, because the effect of sport programs on levels of adiponectin has not been reported identically (Simpson *et al.*, 2008). Moderate to severe intensity exercise training improves blood adiponectin concentrations (Simpson *et al.*, 2008). In diabetic's patients and insulin resistant subjects, exercise has been suggested as a non-pharmacologic treatment for increasing blood circulation adiponectin and improvement of insulin sensitivity (Sigal *et al.*, 2006). Also, following an 8-week training program in form of swimming in diabetic mice, a significant increase was observed in levels of adiponectin and its mRNA gene expression in visceral fat tissue (Tang *et al.*, 2005). In another study, however, insulin sensitivity and insulin resistance improvement caused by weight loss has been attributed to other cytokines secreted by adipose tissue rather than changes in adiponectin. This researcher stated that insulin sensitivity improves independently of the changes in adiponectin caused by exercise training (Simpson *et al.*, 2008).

In a recent study, despite the increased insulin action after long-term endurance training program, no change in adiponectin levels was observed (Hulver *et al.*, 2002). Research evidence shows that despite an increase in blood adiponectin levels after exercise training especially prolonged exercise in some studies, certain findings indicate no change in the levels of this lipid hormone; even in case of weight loss or improvement of body composition and there is not yet a final and inclusive viewpoint in this regard. Therefore, this study has also compared the baselines levels of this peptide hormone and some other diabetic determinative factors such as glucose or lipid profile between diabetic patients and healthy individuals, and evaluates the effects of a long-term aerobic exercise program on the serum level of this peptide hormone and the other mentioned variables.

Material and methods

This study semi-experimental was approved by the ethic committee of Islamic Azad University of Saveh branch. This study was conducted on thirty adult obese males aged 38 – 50 years with type 2 diabetes in Saveh County that divided randomly into two experimental and control groups. Also, a group of healthy non-diabetic obese patients with similar physical characteristics (n = 15), participated in the study to compare baseline levels of biochemical indices with diabetic patients. The diabetic and healthy subjects were nonsmokers and non-athletes as they had not participated in any regular exercise program for the past 6 months. Subjects with a history or clinical evidence of myocardial infarction, congestive heart failure, liver or kidney disease, growth hormone deficiency, neuroendocrine tumor, anemia, or who were on medications known to alter insulin sensitivity were excluded. Informed consent was obtained from each subject after full explanation of the purpose, nature and risk of all procedures used. An obesity criterion for the study was BMI of above 29. Height and anthropometric indices of all participants were measured and recorded at the University Laboratory of Physiology. After measuring anthropometric indices and other initial data, all patients as well as healthy ones appeared for blood sampling between 8-9 a.m. after a 12-h overnight fast, and 8 cc of blood was taken from the brachial vein to measure serum adiponectin, insulin and fasting glucose.

All healthy and diabetic individuals were recommended to avoid using medications affecting carbohydrate and lipid metabolism for at least 24 hours before sampling. All healthy and diabetic individuals were recommended not to participate in any serious physical activity for at least 48 hours before sampling. Those patients who, according to specialist physician, were not able to refrain from taking blood sugar reducing medication for 12 hours before sampling, were excluded from the study.

Blood sampling in the healthy group was only done in order to compare with the baseline levels of serum adiponectin and insulin sensitivity in diabetic

patients studied. After sampling, the diabetics in the experimental group participated in a long term aerobic exercise program (3 sessions/wk for 12 wk) at 50–70%heart rate reserve. The first sessions were of least intensity but the intensity and volume of exercise were gradually added in next sessions.

Typical exercise sessions consisted of a 5-min warm-up of light stretching, 45 min of aerobic training in the form of running or stationary cycling at 50–70%heart rate reserve, and 5–10 min of cool down activity. Diabetic control group did not participate in the training program during this three month period. Finally, 48 hours after the last exercise session, anthropometric indices were measured and blood sampling was done on diabetic patients in the control and experimental group to determine the effect of exercise program on biochemical indexes. Using the values of fasting insulin and glucose, insulin sensitivity was measured in each patient (Katz *et al.*, 2000).

Biochemical analysis

Plasma glucose was determined by enzymatic (glucose oxidase-amino antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran), the Intra-assay and inter-assay coefficient of variation and sensitivity of the method were 1.74%, 1.19% and 5 mg/dL, respectively. Serums were immediately separated and stored at -80° until the assays were performed. Serum insulin (Demeditec Company, Germany) and adiponectin (Biovendor Company, Czech) was determined by ELISA method. The Intra-assay and inter-assay coefficient of variation and sensitivity of the method of insulin were 2.6%, 2.88% and 1.76 μ IU/ml respectively. Also, The Intra-assay and inter-assay coefficient of variation and sensitivity of the method of adiponectin were 5.9%, 6.3% and 0.47 μ g/ml respectively.

Statistical analysis

Statistical analysis was performed with the SPSS software version 15.0 using an Independent paired T-Test. A p-value < 0.05 was considered to be statistically significant.

Results

In this study, the levels of serum adiponectin, insulin and fasting glucose as well as insulin resistance in type-2 diabetics have been compared with those in healthy individuals. In addition, the effect of the three-month aerobic exercise program on these variables and on anthropometric indexes was studied in these patients. Table 1 presents the anthropometric, physiologic and biochemical indexes in health individuals and these variables in

before and after the exercise program in diabetic subjects. All data are expressed as mean \pm SD. Based on this data, the findings of independent t-test showed that adiponectin levels in diabetic patients were significantly lower than those in healthy individuals ($p < 0.05$). Fasting glucose concentration and insulin sensitivity in diabetic patients were higher than in those in healthy individuals ($p < 0.05$).

Table 1. Mean and standard deviation of anthropometrical and biochemical variables of healthy and diabetic groups in baseline and after intervention.

Group Variable	Healthy (baseline)	Experimental diabetic		Control diabetic	
		Pretest	post-test	Pretest	post-test
Weight (kg)	71 \pm 6	95 \pm 8	88 \pm 7	93 \pm 6	94 \pm 7
Height (cm)	174 \pm 8	173 \pm 7	173 \pm 7	172 \pm 6	172 \pm 6
Age (year)	44 \pm 6	44 \pm 6	44 \pm 6	43 \pm 7	43 \pm 7
Waist circumference (cm)	87 \pm 5.14	104 \pm 8	99 \pm 6	105 \pm 7	104 \pm 8
BMI (kg/m ²)	23 \pm 3	31.74 \pm 2.31	29.23 \pm 3.11	31.43 \pm 2.62	31.77 \pm 2.98
Body fat (%)	19 \pm 2.44	28.74 \pm 3.69	24.11 \pm 3.23	29.31 \pm 4.11	29.89 \pm 3.68
Glucose (mg/dl)	97 \pm 11	231 \pm 41	185 \pm 34	235 \pm 41	229 \pm 51
Insulin sensitivity	0.64 \pm 0.09	0.49 \pm 0.08	0.52 \pm 0.07	0.49 \pm 0.09	0.49 \pm 0.11
Insulin (μ IU/ml)	6.44 \pm 0.89	8.56 \pm 2.10	8.18 \pm 2.54	8.14 \pm 2.34	8.72 \pm 2.69
Adiponectin (ng/ml)	8.96 \pm 2.65	6.88 \pm 2.11	5.08 \pm 2.32	6.54 \pm 2.01	6.42 \pm 2.65

The levels of biochemical variables and anthropometric indexes in the two diabetic control and experimental groups were similar ($p \geq 0.05$). On the other hand, the paired t-test findings indicated a significant increase in serum adiponectin caused by three-month exercise program in diabetic experimental group ($p = 0.034$, Figure 1). Serum insulin concentration was not changed by aerobic exercise ($p = 0.340$). All anthropometric indices such as BMI, percentage of body fat and abdominal circumference significantly decreased after exercise training program ($p < 0.05$). Fasting glucose concentration also decreased in the experimental group ($p = 0.000$, Figure 2). Insulin sensitivity in diabetics also increased significantly following aerobic exercise ($p = 0.023$, Figure 3). All anthropometric and biochemical variables remained without change in diabetic control group ($P > 0.05$).

Discussion

Lifestyle changes such as weight loss, regular aerobic exercise are regarded as non-pharmaceutical interference effective on the metabolic and cardiovascular risk factors (Braith *et al.*, 2006). In addition to its function as fat reserve and heat insulation, adipose tissue as an endocrine organ also secretes biologic active cytokines called adipokines, and dysfunction at systemic level of which is associated with metabolic syndrome, cardiovascular diseases and type 2 diabetes (Izquierdo *et al.*, 2001). Statistical findings of this study showed that an adiponectin level in type 2 diabetic patients is far lower than in healthy individuals. The patients were also of lower insulin sensitivity and higher fasting glucose levels compared to the healthy group. Decrease of adiponectin and insulin sensitivity and hyperglycemia phenomenon have also been reported in most other studies. With this regard, research

evidence has revealed that adiponectin indirectly or indirectly augments insulin sensitivity and inflammatory mediators such as C reactive protein, Interleukin-6 and Tumor factor necrosis alpha (Berg *et al.*, 2005). Increased levels of systemic adiponectin increase glucose uptake into skeletal muscle and fat oxidation (Vivian *et al.*, 2007). Insulin-like property of adiponectin has indicated that this peptide hormone is effective to improve metabolic abnormalities and hyperglycemia associated with obesity and type 2 diabetes (Vivian *et al.*, 2007). Like insulin, the effect of exercise on adiponectin also leads to accelerate or increase blood glucose uptake or increased fat oxidation (Brooks *et al.*, 2007).

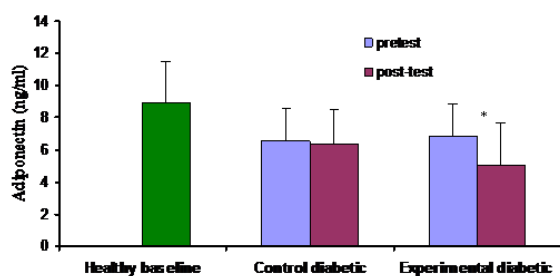


Fig. 1. The baseline serum adiponectin in healthy and diabetic group and its change after intervention in diabetic patients. Serum adiponectin concentrations of experimental group increased significantly after aerobic exercise program.

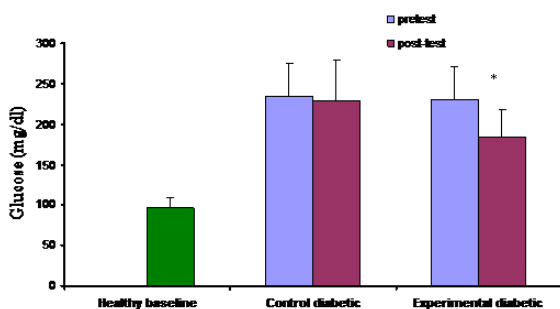


Fig. 2. The baseline glucose concentration in healthy and diabetic group and its change after intervention in diabetic patients. Fasting glucose concentrations of experimental group decreased significantly after aerobic exercise program.

It is known that an increase in visceral fat tissue is a better predictor than other anthropometric indexes for diagnosing insulin resistance, type 2 diabetes and cardiovascular diseases. The findings of this study

showed that adiponectin has an inverse relationship with visceral fat in the studied diabetic patients. In other words, increased visceral fat is associated with reduced systemic adiponectin. The most important finding of this study was the increase of adiponectin serum levels by three-month exercise in diabetic experimental group. The aerobic exercise led to a 34% increase in adiponectin serum of diabetics and these findings were observed while the sedentary diabetic group experienced no change in adiponectin. In confirmation of these findings, after 16 weeks of exercise in a recent study, a significant increase was observed in insulin sensitivity and plasma adiponectin in 62 type 2 diabetic patients (Brooks *et al.*, 2007). In another study, 4 weeks of training by people with diabetes resulted in a significant reduction in body weight together with significant increase in plasma adiponectin (Oberbach *et al.*, 2006).

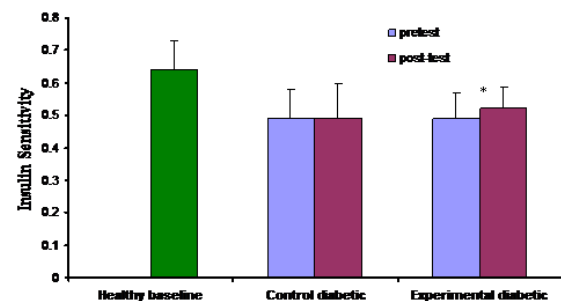


Fig. 3. The baseline insulin sensitivity in healthy and diabetic group and its change after intervention in diabetic patients. Insulin sensitivity in experimental group increased significantly after aerobic exercise program.

In our study, increased levels of adiponectin were associated with a significant reduction in fasting glucose. In this case, the findings point out that adiponectin, leads to increased glucose metabolism especially in skeletal muscle (Imbeault, 2007). Furthermore, by decreasing hepatic glucose production through direct inhibition of hepatic gluconeogenesis enzymes i.e. *Phosphoenolpyruvate* carboxykinase and *Glucose 6-phosphate*, adiponectin contributes to reduction of blood glucose and improvement of insulin sensitivity and glycemic control (Yamauchi *et al.*, 2002). This anti-

inflammatory cytokine increases oxidation of fatty acids in skeletal muscles and reduces delivery of unsaturated fatty acid to the liver which in turn leads to decreased synthesis of hepatic triglyceride and secretion of vLDL (Julius, 2003). Another finding of this study is the increase of insulin sensitivity through exercise. Researchers have attributed the increased insulin sensitivity after exercise to increased levels of blood adiponectin (Lara-Castro *et al.*, 2006). Existing evidence indicate that the relation between aerobic exercise and increased insulin sensitivity caused by adiponectin most probably depends on the degree of expression of adiponectin receptors in the related skeletal muscles (Vivian *et al.*, 2007). Researchers attributed one of the mechanisms of increasing insulin function due to exercise to increased capillary density between muscle fibers and improved insulin intercellular signals (Nakai *et al.*, 2002).

Multiple confounding factors such as diet, exercise duration and intensity and changes in body fat levels are effective in changes of systemic adiponectin levels caused by exercise training. In this regard, several studies have observed the increase of the expression of adiponectin receptors in skeletal muscle of humans and animal models. These studies have reported that the increase of adiponectin levels and the expression of adiponectin receptors vary depending on the intensity and the length of the exercise (Bluher *et al.*, 2006). In this regard, Zang *et al.* contend that changes in adiponectin levels depend on the intensity and the length of the exercise (Zeng *et al.*, 2007). Some other studies, however, maintain that adiponectin increase occurs only when the exercise program or diet leads to weight loss or decrease of fat mass. In our study, serum adiponectin decrease was associated with weight loss and reduction of body fat mass and body mass index. Nevertheless, in spite of the said findings, a recent study indicated that 4 weeks of aerobic exercise resulted in a 97% increase of adiponectin in obese and 86% increase of adiponectin in type-2 diabetics without any significant weight loss (Bluher *et al.*, 2006). In another study, following a 10-week aerobic

exercise program, a two-fold increase in adiponectin was observed in the absence of weight loss (Kriketos *et al.*, 2004). Some researchers have pointed to the fact that lack of increase in blood adiponectin caused by exercise may be due to the simultaneous increase of other cytokines and hormones effective in reducing levels of adiponectin (Fasshauer *et al.*, 2003).

Conclusion

In an overall conclusion, it can be said that adiponectin levels and insulin sensitivity are lower in diabetic patients in than in healthy people. Exercise an effective non-pharmaceutical treatment for increasing adiponectin levels and reduction of hyperglycemia in type-2 diabetic patients. Although the basic mechanisms involved in the adiponectin levels through exercise are not yet fully known, but it seems that loss of weight and body fat mass and also negative energy balance, have a significant impact on adiponectin increase. However, taking into consideration the findings of other studies, it appears that change in other confounding factors such as other cytokines and changes in volume of plasma are effective in adiponectin response to exercise and requires further studies.

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